Remarks

Claims 1-4 are pending in the application. Claims 1 and 2 have been amended. Support for the claim amendments can be found throughout the application, including the claims as originally filed. Importantly, no new matter has been added to the claims. The amendment to the claims should not be construed to be an acquiescence to any of the rejections. The amendments to the claims are being made solely to put the claims in proper format to expedite the prosecution of the above-identified application. The Applicant reserves the right to further prosecute the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 USC § 120.

Response to Rejections under 35 U.S.C. § 102(a)

Claims 1, 3 and 4 stand rejected under 35 U.S.C. § 102(a) based on the Examiner's contention that they are anticipated by Kim et al. (U.S. Patent No. 5,723,147). The Applicants traverse this rejection.

Kim et al. discloses a process of preparing a biologically active agent encapsulated within a multivesicular liposome comprising the steps:

a) dissolving in one or more organic solvents a lipid component containing at least one neutral lipid and at least one amphipathic lipid;

b) adding into the lipid component an immiscible first aqueous component containing one or more biologically active substances to be encapsulated;

c) adding a hydrochloride to either or both the first aqueous component and the lipid component, forming a water-in-oil emulsion from the two immiscible components;

d) dispersing the water-in-oil emulsion with a second aqueous component to form solvent spherules containing in them multiple droplets of the first aqueous component; and

e) removing the organic solvents, such as by evaporation. See col. 1, ll. 37-51.

The term hydrochloride is described as being hydrochloric acid or other hydrochlorides such lysine hydrochloride. See col. 3, ll. 51-56. It is the Examiner's contention that lysine is a complexing agent. The Applicants' traverse this contention.

The role of lysine, when it is used, in Kim et al.'s disclosure is to control pH. It does not complex with the bioactive agent as does the complexing agents of the present invention.

The role of the complexing agent in the present application as described on page 16, lines 11-15, of the specification is to change the physical properties of the bioactive agent primarily decreasing the solubility and precipitating the bioactive agent. Because this is the role of the complexing agent, it is crucial that the claimed methods form an emulsion before the complexing agent and bioactive agent react. Otherwise, the bioactive agent would precipitate and not be encapsulated in a liposome.

This is not the case in Kim et al. where the hydrochloride used does not affect the solubility of the bioactive agent. This is why in the steps disclosed in Kim et al., the hydrochloride and bioactive agent are allowed to react before the emulsion forms. In the process disclosed in Kim et al., there is no danger of precipitating the bioactive agent with the hydrochlorides so the two reagents can react before forming the emulsion. See col. 5, ll. 7-15, where the hydrochloride and bioactive agent are mixed in an aqueous phase before forming an emulsion, and col. 6, ll. 14-23, where it states that generally the bioactive agent and hydrochloride may be added together in the first aqueous phase. Contrast this teaching with step b) of either present claim 1 or 2, where an emulsion forms comprising the lipid and bioactive agent (claim 1) or lipid and complexing agent (claim 2) *before* adding either the complexing agent or bioactive agent in step c), respectively. If this was not the case, the bioactive agent would begin to precipitate as a bioactive complex before encapsulation within the liposome and high encapsulating levels would not be obtained.

Also note in the specification that wherever a lysine is mentioned as an example of a complexing agent it is always as a *poly*lysine. See, for example, page 5, l. 21 and 23; page 23, l. 17; page 26, l. 29; and page 28, l. 4. A lysine molecule would not have the

size increasing effects that polylysine has and no precipitation would occur.

It is clear from Kim et al. that the role of the hydrochloride is to affect pH and not to complex with the bioactive agent. See col. 5, ll. 58-66. It is not a complexing agent as the Examiner contends. Because Kim et al. does not disclose a complexing agent limitation, Kim et al. does not disclose each and every limitation of the claims.

Accordingly, the Applicants respectfully request the withdrawal of the rejections based on 35 U.S.C. § 102(a).

Response to Rejections under 35 U.S.C. § 102(b)

Claim 1 stands rejected under 35 U.S.C. § 102(b) based on the Examiner's contention that it is anticipated by Kim et al. (Cancer Research, **1993**, *53*, 1596-1598). The Applicants traverse this rejection.

As was the case with U.S. Patent No. 5,723,147 to Kim et al., the Kim et al. Cancer Research paper does not disclose a complexing agent. The lysine in the Cancer Research paper acts as a buffer and not a complexing agent. As is clear from a fair reading of either the Kim et al. patent or Kim et al. Cancer Research paper, the role of the HCl is to lower the pH to such a degree that every available Lewis Base is either neutral or cationic (see page 1596, line 15-16 where the pH is lowered to 1.1). In such an environment there would be no complexing occuring.

Because Kim et al. in the Cancer Research Paper does not disclose a complexing agent, it does not anticipate each and every limitation of the claim.

Accordingly, the Applicants respectfully request the withdrawal of the rejections based on 35 U.S.C. § 102(b).

Response to Rejections under 35 U.S.C. § 103(a)

Kim et al. (U.S. Patent No. 5,723,147)

Claim 2 stands rejected under 35 U.S.C. § 103(a) based on the Examiner's contention that it is obvious over Kim et al. (U.S. Patent No. 5,723,147). The applicants traverse this rejection.

Claim 2 differs from claim 1 in that an emulsion comprising a lipid and a

complexing agent is prepared before adding a bioactive agent, instead of as in claim 1 where an emulsion between a lipid and a bioactive agent is formed before adding a complexing agent.

However, as discussed above, Kim et al. does not teach a method of preparing a lipid encapsulated bioactive agent comprising a complexing agent. One of ordinary skill in the art would know from a fair reading of Kim et al., especially where the preferred hydrochloride is HCl, see col. 5, l. 37, that the role of the hydrochloride, even when it is lysine hydrochloride, is to lower the pH and not complex with the bioactive agent. The hydrochloride does not complex with the bioactive agent as in the present invention because some of the bioactive agent would precipitate when the two reagents react in the absence of the lipid emulsion. It would not be obvious from Kim et al. to use a complexing agent because to use one in place of the lysine hydrochloride would result in precipitation of the bioactive agent and inefficient encapsulation.

Because Kim et al. does not teach each and every limitation of claim 2, the Applicants request the withdrawal of the rejection of claim 2 under 35 U.S.C. § 103(a).

Kim et al. (U.S. Patent No. 5,759,573)

Claims 1-4 stand rejected based on the Examiner's contention that they are obvious under 35 U.S.C. 103(a) over Kim et al. (U.S. Patent No. 5,759,573). The Applicants traverse this rejection.

The method disclosed by Kim et al. in U.S. Patent No. 5,759,573 is similar to the method disclosed in Kim et al. in the Cancer Research Paper (see Example 1). Importantly, the method disclosed in Kim et al. in U.S. Patent No. 5,759,573 first reacts the bioactive agent with cyclodextrin in an aqueous phase. This aqueous phase is then added to a lipid-chloroform solution. This is very different from the presently claimed methods where it is crucial that an emulsion comprising a lipid and either the bioactive agent (claim 1) or complexing agent (claim 2) is formed first before adding the complexing agent or bioactive agent, respectively. This again is because of the nature of the presently claimed complexing agent and the extent to which it alters the physical properties of the bioactive agent. If the emulsion is not formed before the complexing

and bioactive agent react, then at least some of the bioactive agent will be lost due to precipitation and high encapsulations will not be achieved.

Unlike the complexing agents of the present invention that alter the physical properties of the bioactive agent, cyclodextrin of Kim et al. acts more like an additional lipid. Cyclodextrin is a cyclic oligomer containing anywhere from 6 to 12 glucose units. The hydrophilic hydroxy groups of the glucose units are directed toward the outside of the molecule leaving a hydrophobic cavity. See col. 4, ll. 48-60. The bioactive agent is associated with the hydrophobic cavity in the same way it is associated with the hydrophobic moiety of a lipid, but it does not form a complex with the cyclodextrin in the same manner as the complexing agents of the present invention. If it did at least some of the bioactive agent would be lost to condensation in the first step where the two are allowed to react in the absence of the lipid emulsion.

The Applicants disagree with the Examiner's assertion that it would have been obvious to one of ordinary skill in the art to mix the complexing agent and the bioactive agent from two different phases based on Kim et al. teaching mixing cyclodextrin and a bioactive agent together in the same phase "because one of ordinary skill in the art would reasonably expect the complexation between the active agent and the complexing agent to occur, irrespective of whether they are added together in the same phase or separately in two different phases." This assertion misses a key aspect of the present invention which is the nature of the complexing agent. Kim et al. does not disclose a complexing agent as presently claimed and the Examiner has not supplied any motivation why one of ordinary skill in the art would substitute the cyclodextrin of Kim et al. with the complexing agent of the present claims. In fact one of ordinary skill in the art would not be motivated to do so because he or she would lose at least some of the bioactive agent to precipitation according to the steps taught by Kim et al.

Because Kim et al. teaches using cyclodextrin and not a complexing agent of the present claims, the Applicants request the withdrawal of the 35 U.S.C. 103(a) rejection of claims 1-4.

Fees

The Applicants believe they have provided for the required fees in connection with the filing of this paper. Nevertheless, the Director is hereby authorized to charge any additional required fee to our Deposit Account, **06-1448**.

Conclusion

For the foregoing reasons, the Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the pending claims are now in condition for allowance and early notification to this effect is earnestly solicited. If any questions are raised by this Amendment and Response, the Examiner is urged to contact the undersigned at the telephone number listed below.

Respectfully submitted,
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